

## MGE Enhancers to Select for Interneuron Precursors Produced from Human ES Cells

### Grant Award Details

MGE Enhancers to Select for Interneuron Precursors Produced from Human ES Cells

**Grant Type:** Basic Biology II

**Grant Number:** RB2-01602

**Project Objective:**

- A) Identify and characterize enhancers that drive expression at specific developmental stages as human stem cells mature into cortical interneurons.
- B) Use the "MGE" enhancers to assay and select for desired cell states as human ES-derived stem cells mature into cortical interneurons by driving the expression of reporters including EGFP/rCherry and antibiotic resistance enzymes
- C) Identify antibodies that recognize antigens on the surface of differentiating human interneurons and human stem cells as they mature into cortical interneurons; the antibodies will be useful for cell sorting/purification.

**Investigator:**

<b>Name:</b>	John Rubenstein
<b>Institution:</b>	University of California, San Francisco
<b>Type:</b>	PI

**Disease Focus:** Epilepsy, Neurological Disorders

**Human Stem Cell Use:** Embryonic Stem Cell

**Award Value:** \$1,387,800

**Status:** Closed

### Progress Reports

**Reporting Period:** Year 1

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**Reporting Period:** Year 2

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**Reporting Period:** Year 3

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## Grant Application Details

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**Application Title:** MGE Enhancers to Select for Interneuron Precursors Produced from Human ES Cells

**Public Abstract:** There are now viable experimental approaches to elucidate the genetic and molecular mechanisms that underlie severe brain disorders through the generation of stem cells, called iPS cells, from the skin of patients. Scientists are now challenged to develop methods to program iPS cells to become the specific types of brain cells that are most relevant to each specific brain disease. For instance, there is evidence that defects in cortical interneurons contribute to epilepsy, autism and schizophrenia. The experiments proposed in this grant application aim to understand basic mechanisms that underlie the development of cortical interneurons. We are discovering regulatory elements (called enhancers) in the human genome that control gene expression in developing interneurons. We have three experimental Aims. In Aim 1, we will study when and where these enhancers are expressed during mouse brain development. We will concentrate on identifying enhancers that control gene expression during development of specific types of cortical interneurons, although we hope to use this approach for additional cell types. Once we identify and characterize where and when these enhancers are active, in Aim 2 we will use the enhancers as tools in human stem cells to produce specific types of cortical interneurons in the test tube. The enhancers will be used to express proteins in the stem cells that will enable us purify only those cells that have specific properties (e.g. properties of cortical interneurons). In Aim 3 we will explore whether the human brain produces cortical interneurons in the same way as the mouse brain; this information is essential to identify molecular markers on the developing interneurons that could be used for further characterization and purification of the interneurons that we are generating in Aim 2. We want to emphasize that while the experiments focus on cortical interneuron subtypes, our work has general implications for the other types of brain cells our labs study, such as cortical and striatal neurons. In sum, the basic science mechanisms that we will discover will provide novel insights into how to generate specific types of neurons that can be used to study and treat brain diseases.

**Statement of Benefit to California:**

Large numbers of California residents are stricken with severe medical disorders affecting the function of their brain. These include epilepsy, Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, Autism and Schizophrenia. For instance, a recent report from the Center for Disease Control and Prevention [[www.cdc.gov/epilepsy/](http://www.cdc.gov/epilepsy/)] estimates that 1 out of 100 adults have epilepsy. In California, epilepsy is one of the most common disabling neurological conditions, with approximately 140,000 affected individuals. The annual cost estimates to treat epilepsy range from \$12 to \$16 billion in the U.S. Currently up to one-third of these patients are not receiving adequate treatment, and may benefit from a cell-based transplantation therapy that we are currently exploring with our work in mice.

There are now viable experimental approaches to elucidate the genetic and molecular mechanisms that underlie these neuropsychiatric disorders through the generation a stem cells, called iPS cells, from the skin of patients. Scientists are now challenged to develop methods to program iPS cells to become the specific types of brain cells that are most relevant to each specific brain disease. For instance, there is evidence that defects in cortical interneurons contribute to epilepsy, autism and schizophrenia. The experiments proposed in this grant application aim to understand basic mechanisms that underlie the development of cortical interneurons. We are discovering regulatory elements (called enhancers) in the human genome that control gene expression in developing interneurons. Our experiments will help us understand fundamental mechanisms that govern development of these cells. Furthermore, we have designed experiments that harness these enhancers to drive the production of specific subtypes of these cells from human stem cells. This will open the door to making these types of neurons from iPS cells to study human disease, and potentially to the production of these neurons for transplantation into patients whose interneurons are deficient in regulating their brain function. Furthermore, the approach we describe is general and readily applicable to the generation of other brain cells. Thus, the results from these studies will provide essential and novel basic information for understanding and potentially treating severe brain disorders.

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